R E M A R K S

Applicants again want to thank the examiner for conducting an interview with applicants' representative. During the interview, the method of claim 33 and the disclosure of US patent 6,750,224 and WO 00/68229 were discussed.

Claims 33 and 47 are in this application. Claims 1-32, 34- 46 and 48 have been cancelled.

Applicants preserve all rights to file one or more divisional applications directed to any subject matter disclosed in this application and not presently claimed.

The Examiner states that claim 33 is rejected under 35 USC 102(e) as being anticipated by Patel et al. (US Patent 6,750,224). This is respectfully traversed.

In order for a reference to anticipate a claim, each and every element of the claimed invention must be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). As shown in the chart below, each and every element of claim 33 is not disclosed in US patent 6,750,224. In particular, claim 33 claims a method for enhancing optical purity of of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid L-arginine salt comprising, the steps of

(a) suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water and organic solvent selected from acetone or acetonitrile to form a suspension,

(b) adding an equimolar quantity of L-arginine to the suspension and heating the suspension to a temperature between about 40 to 70°C to obtain a clear solution,
(c) adding 2 to 3 times more of the organic solvent added in step (a),
(d) cooling the solution to 0 to 45°C, for 1 hr to 5 hr, to effect the crystallization;
(e) isolating the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl -1-oxo-1H,5 H-benzo[i,j]quinolizine-2- carboxylic acid L-arginine salt at below 35°C by filtration, and
(f) drying the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine -2-carboxylic acid L-arginine salt.

Lines 10-35 of column 15 of US patent 6,750,224 discloses a process for preparing hydrates of the S-(-) isomer of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid. As shown in the side by side comparison in the table below, there is no disclosure in lines 10-35 of column 15 of US patent 6,750,224 of a method for purifying a racemic mixture nor any disclosure of preparing an amino acid salt.

Claim 33 of '040 application	US patent 6,750,224 col. 15, lines 12-25	US patent 6,750,224 col. 15, lines 25-35	US patent 6,750,224 col. 15, lines 36-44	US patent 6,750,224 col. 15, lines 45-54

A method for enhancing optical purity of of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt comprising, the steps of:	A method for preparing a hydrate of Formula I col. 15, lines12-15 (hydrates of formula I may be prepared by changing recrystallization conditions, and the temperature/vacuum conditions.)			

(a) suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water and organic solvent selected from acetone or acetonitrile to form a suspension,	preparing 0.2 hydrate by dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in a minimum volume of organic solvent, preferably acetonitrile or ethanol at an elevated temperature, preferably at the reflux temperature of the solvent	preparing 0.2 hydrate by dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in alkali, preferably 1 molar aqueous sodium hydroxide, heating to 55-60°C.	preparing 0.5 hydrate by dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in a minimum volume of organic solvent, such as acetone at reflux temperature,	preparing 0.75 hydrate by dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water, preferably at 10% (weight by volume) suspension, formulating into a slurry by vigorous stirring continuing stirring at 5°C for 1-2 hours,

(b) adding an equimolar quantity of L-arginine to the suspension and heating the suspension to a temperature between about 40 to 70°C to obtain a clear solution,		acidifying, preferably with concentrated hydrochloric acid, at 55-60°C, maintaining the suspension at 50-70°C., preferably at 60°C for at least 30 minutes		adding acetone ca. 5% (weight by volume) with continuation of stirring at 5°C for 4-5 hours,
(c) adding 2 to 3 times more of the organic solvent added in step (a),	and adding an amount of water sufficient to bring about crystallization			
(d) cooling the solution to 0 to 45°C, for 1 hr to 5 hr, to effect the crystallization;	after cooling in high yields,	cooling,	adding an appropriate amount of water at ambient temperature, sufficient to bring about crystallization after cooling in high yields,	

(e) isolating the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl -1-oxo-1H, 5 H-benzo[i, j]quinolizine-2-carboxylic acid L-arginine salt at below 35°C by filtration, and	filtering and	filtering, washing with water and	filtering and	filtering and
(f) drying the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt.	drying the separated crystals at temperatures up to 40-50°C for 3-6 hours, preferably 5 hours, in vacuo up to 50 mm of Hg to constant weight.	drying the separated separated crystals at temperatures up to 40-50°C for 3-6 hours, preferably 5 hours, in vacuo up to 50 mm of Hg to constant weight.	drying the separated crystals at temperatures up to <40°C for 3-6 hours, preferably 5 hours, to a constant weight.	drying the product at temperatures <40°C for 3-6 hours, preferably 5 hours, to a constant weight.

Therefore, since each element of claim 33 is not disclosed in US patent 6,750,224, claim 33 is not

anticipated by the patent.

It is respectfully requested that the rejection be withdrawn.

According to the Official Action, claims 33 and 47 are rejected as being obvious over claims 8 and 9 of WO 00/68229 in view of Kwan. Applicants respectfully traverse this rejection.

Claim 33	Example 7 of WO 00/68229	Example 8 of WO 00/68229
A method for enhancing optical purity of of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt comprising, the steps of:	Preparation of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, L-arginine salt 0.25 hydrate.	Preparation of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, L-arginine salt 0.75 hydrate.
(a) suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water and organic solvent selected from acetone or acetonitrile to form a suspension,	Aqueous L-arginine is added to a stirred solution of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid in methanol.	L-(+) Arginine is added in portions to a suspension solution of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, L-arginine salt 0.2 hydrate in methanol.

(b) adding an equimolar quantity of L-arginine to the suspension and heating the suspension to a temperature between about 40 to 70°C to obtain a clear solution,	The solution is stirred for 30 min., passed through a microfilter and concentrated to dryness to furnish S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, L-arginine salt.	The solution is concentrated in a vacuum to give the desired product as a yellow solid which was dried at 50°C at 55 mm/Hg for 5 hours.
(c) adding 2 to 3 times more of the organic solvent added in step (a),		
(d) cooling the solution to 0 to 45°C, for 1 hr to 5 hr, to effect the crystallization;		
(e) isolating the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt at below 35°C by filtration, and		

(f) drying the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt.		

As can be seen by the table above, the method of claim 33 is a method for enhancing optical purity of of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid L-arginine salt comprises a multi-step process that differs and is not obvious from examples 7 and 8 of WO 00/68229. The process of claim 33 requires suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water and organic solvent. The processes of examples 8 and 9 begin with the (S) isomer and the purpose of the processes described in these examples is not the same as the process of claim 33. In the process of claim 33, additional organic solvent is added after the addition of L-arginine with the organic solvent being acetone or acetonitrile. In the process of examples 7 and 8 the solution is not heated after the addition of L-arginine and therefore, no cooling step is required.

Claim 33	Claim 8 of WO 00/68229	Claim 9 of WO 00/68229
A method for enhancing optical purity of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt comprising, the steps of:	A process for the preparation of the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate which comprises	A process for the preparation of the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.5 hydrate which comprises

(a) suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid in water and organic solvent selected from acetone or acetonitrile to form a suspension,	dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid in a minimum volume of organic solvent, at an elevated temperature	dissolving S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid in a minimum volume of organic solvent, at reflux temperature
(b) adding an equimolar quantity of L-arginine to the suspension and heating the suspension to a temperature between about 40 to 70°C to obtain a clear solution,		
(c) adding 2 to 3 times more of the organic solvent added in step (a),		
(d) cooling the solution to 0 to 45°C, for 1 hr to 5 hr, to effect the crystallization;	adding an amount of water sufficient to bring about crystallization after cooling in high yields	adding an amount of water at ambient temperature sufficient to bring about crystallization after cooling in high yields

(e) isolating the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt at below 35°C by filtration, and	filtering and drying the separated crystals at temperatures up to 40-50°C for 3-6 hours, in vacuo upto 50 mm of Hg to a constant weight.	Filtering and drying the separated crystals at temperatures up to 40-50°C for 3-6 hours.
(f) drying the crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid L-arginine salt.		

The processes of claims 8 and 9 of WO 00/68229 differ from the process of claim 33. As stated above the process of claim 33 is a method for enhancing optical purity of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid L-arginine salt. The process of claims 8 and 9 are processes for preparing hydrates of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid and not a process for preparing enhancing the optical purity of 6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid L-arginine salt. L-arginine is not used in the processes of claims 8 and 9 and the S-(-) isomer of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2- carboxylic acid is dissolved in a minimum of organic solvent. The process of claim 33 requires suspending a partially optically impure mixture of 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H, 5H-benzo[i,j] quinolizine-2-carboxylic acid in water and organic solvent.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). There is no disclosure or suggestion in WO 00/68229 either alone or in combination with Kwan that would lead one skilled in the art to the claimed process.

It is respectfully requested that this rejection be withdrawn.

It is respectfully submitted that this application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully
submitted,

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